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THE ACTION ON DOGS OF THE TOXIC SUBSTANCE OBTAINABLE FROM VIRULENT PNEUMOCOCCI AND PNEUMONIC LUNGS.*

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From the work of Gay and Auer and Lewis,¹ Schultz and Jordan² and others we know that death in guinea-pigs in immediate anaphylaxis is due to bronchial spasm, and there is no doubt that death is due to the same cause after injections of peptone, of "anaphylatoxin," and of the toxic material obtainable on autolysis in NaCl solution of various bacteria.

Biedl and Kraus,³ Pearce and Eisenbrey,⁴ and others have shown that the marked fall in blood-pressure is the important symptom in anaphylaxis in dogs and that the other symptoms, writhing, vomiting, defecation, urination, and prostration, are secondary to anemia of the brain. Schittenhelm and Weichardt⁵ have called particular attention to the lesions found in the intestines in anaphylaxis in dogs, and name the condition "enteritis anaphylactica."

In previous studies one of us⁶ has shown that autolytic extracts of various bacteria, especially pneumococci, produce in normal guinea-pigs symptoms typical of immediate anaphylaxis. The extracts are, relatively speaking, nontoxic at first, very toxic at a certain period, and become nontoxic after being kept at 37° C. This condition is associated with proteolysis. It has been shown further that the symptoms in guinea-pigs caused by autolytic extracts of pneumococci in no way differ from those observed following the injection of toxic material from pneumococcus exudates. If it could be shown that the symptoms in dogs following the injection of toxic extracts are more or less typical of

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¹ *Jour. Exper. Med.*, 1910, 12, p. 151.

² *Wien. klin. Wchnschr.*, 1909, 22, p. 363.

³ *Jour. Pharm. and Exper. Therap.*, 1911, 2, p. 375.

⁴ *Jour. Infect. Dis.*, 1910, 7, p. 565.

⁵ *Deutsch. med. Wchnschr.*, 1911, 37, p. 867.

⁶ Rosenow, *Jour. Infect. Dis.*, 1911, 9, p. 190. 1912, 11, p. 235.

anaphylaxis in this species, it would furnish additional evidence that during anaphylaxis there is produced in the animal toxic material similar to that produced *in vitro*.

In the following pages we wish to record briefly the results of experiments in dogs with intravenous injections of various products of pneumococci and pneumococcus exudates.

TECHNIC.

Ether was used as the anesthetic in all of the experiments in which tracings of the blood-pressure and respiration were made. A glass cannula was inserted into the trachea through a median incision and connected with the ether bottle by means of a T-tube. To the small arm of this tube was connected the respiratory tambour. A three-way cannula was placed in the carotid artery after ligation of the vessel distally. One arm of this cannula was connected with a pressure-bottle containing 2 per cent sodium citrate solution. The other arm was connected with the mercury manometer for recording the blood-pressure. The injections were all made into the femoral vein by exposing the vein. Before the injection, complete anesthesia was induced and kept up throughout the experiment. The supply of ether was kept constant by adding sufficient at intervals to keep the level of the liquid the same throughout the experiment. After the completion of the experiment the dog was immediately killed, provided it did not die as a result of the injection, and autopsy made. Sections of the organs were immediately placed in Zenker's fluid. The sections were stained mostly with hematoxylin and eosin, and many sections studied from each organ.

The extracts of pneumococci were prepared from virulent pneumococci which had been recently isolated and cultivated in ascites-meat broth. They were sedimented at high speed and the supernatant broth poured off. The density of the suspensions in NaCl solution was between four and five times that of a dense growth in the broth. For autolysis the pneumococci were suspended for 48 hours in each of two changes of NaCl solution at 37° C., and practically all became gram negative. In the NaCl suspension of living, unautolyzed pneumococci injected in Experiment 3

approximately one-sixth of the cocci had become gram negative at the time of the injection. The extract which was injected into the sensitized dog (Experiment 5), was prepared by placing the suspension of pneumococci in the ice-chest for 48 hours and heating to 60° C. for one hour. It was then centrifugated clear. The extracts of pneumonic lungs were prepared by passing a portion of a freshly obtained lung through a meat chopper, mixing with NaCl solution, and straining through a rather thick layer of sterile cheesecloth. This was then centrifugated at high speed, and the supernatant opalescent fluid used. This is designated as the first extract, while the extract of the sediment thus obtained is designated as the second extract. Only such lungs were used as contained pneumococci in apparently pure culture. Control cultures were made to determine whether the extract was sterile; only sterile extracts were used. The doses for dogs, per gram of body weight, were approximately four-fifths of the average dose for guinea-pigs. It was found necessary to give rather large doses in order to produce striking results. The temperature was taken at intervals throughout the experiment but showed little change. A drop of one-half to one degree Centigrade was noted in the fatal cases. In one of the dogs, which showed marked immediate symptoms, the leukocyte count presented a pronounced drop. The coagulation time of the blood was noted at the end of the experiments. The 10 experiments selected for publication illustrate the results obtained in a larger series. It was noted that gaseous distension and acute dilatation of the stomach were present in those which showed marked symptoms. When this fact was mentioned to Dr. R. T. Woodyatt, he suggested that we test the gas for CO₂. This was done by passing it through lime water. Control tests for fermentation of the stomach contents were placed in the incubator, but in no instance was fermentation observed.

RESULTS.

The results in Experiments 1 and 3 need a word of explanation. The early effect on the blood-pressure in Experiment 1, in which pneumococci partially autolyzed under ether were injected and which contained a large amount of preformed toxic material, is

greater than in Experiment 2, in which live virulent pneumococci were injected. The transient early drop observed in No. 3 is undoubtedly due to free toxic material because some of the pneumococci were gram negative; the hemorrhages and the late effect on the blood-pressure in this experiment are marked. This is what one would expect because unautolyzed live pneumococci undergo destruction *in vivo* in large numbers and hence liberate a proportionately greater amount of toxic material. It is possible too that the late toxic effects were due to bacterial growth. The fact that the more completely autolyzed extract in Experiment 2 and the autolyzed pneumococci in Experiment 4 produced no symptoms, as well as the results of other experiments, speak for the correctness of the view that the toxic material, in the main, is similar whether produced by self-digestion of pneumococci *in vitro* or by lysis *in vivo*.

In studying the protocols and curves it is apparent that the evidence of splanchnic dilatation and intestinal lesions is most marked in the normal animals which showed immediate and pronounced fall in blood-pressure as the result of injection of preformed toxic material, and in sensitized animals following injection of unautolyzed extracts or suspensions of pneumococci. In those injected with the second unautolyzed lung extracts (Experiments 7 and 8), in which the fall in blood-pressure is more gradual and begins one hour after the injection, the intestinal lesions are less pronounced. By injecting suspensions of pneumococci into unetherized, sensitized dogs, and toxic autolysates and toxic extracts from pneumonic lungs in normal dogs, the typical symptoms and findings described by various observers in protein anaphylaxis were obtained in each case. The fact that typical intestinal lesions, the "enteritis anaphylactica" of Schittenhelm and Weichardt, can be produced by preformed toxic material in normal dogs indicates that in anaphylaxis this lesion is due at least in part to marked splanchnic dilatation and not wholly to the formation of toxic material in the intestinal wall, as these authors conclude. The reason that the lesions in the sensitized dog (Experiment 5) are not more pronounced is due to the fact that the extract used contained only a small amount of material from which toxic matter could be

formed. Control injections into unetherized, sensitized dogs of corresponding suspensions of pneumococci produced extremely severe symptoms. A normal dog injected with this unautolyzed heated extract showed no noteworthy symptoms.

The results in Experiments 7, 8, and 10 are interesting. They show that the second extract of pneumonic lungs is not immediately toxic, and not toxic when kept on ice for 24 hours. Both, however, contained material from which toxic products are formed *in vivo*. After this extract was allowed to autolyze under ether for five days (Experiment 10) no immediate symptoms were produced, and the material from which toxic matter was produced previously *in vivo* had then disappeared. Injections of lung extract 649 showed that it was very toxic at once and only slightly toxic at the end of 18 hours when kept at 37° C.; whereas, when new pneumococci were added (Experiment 9), it was highly toxic at the end of 18 hours. Other experiments gave similar results. We realize that extracts of normal lungs and other organs produce similar symptoms, but the fact that addition of pneumococci to these extracts increases the toxicity, and that the toxicity appears and disappears in the same way as in pneumococcus autolysates, makes it clear that the pneumococci play a part.

The hemorrhages were most extreme in the dogs which received the large doses of living virulent pneumococci, the first extract of the pneumonic lungs, and a lung extract to which virulent pneumococci were added and then allowed to autolyze under ether at 37° C. for 18 hours. The dogs which gave no symptoms showed few or no hemorrhages. The perivascular distribution of the hemorrhages in the lung and other organs is particularly interesting. The exact reason for this is not entirely clear, but concentration of toxic material in the vessels—a form of mass action—is probably responsible. The order of frequency in which hemorrhages were found in the viscera is as follows: lungs, heart, kidney, intestines, liver, pancreas, and spleen.

The coagulation time of the blood was markedly delayed, for hours, in the dogs which died as the result of the injections; moderately delayed in the dogs which showed severe symptoms; and unchanged in those which showed no symptoms.

Gaseous distension of stomach, amounting to acute dilatation in Experiments 7 and 9, was present to a greater or less degree in all the animals which showed symptoms. No gas was found in those which showed no symptoms. Carbon dioxid was found present in large amounts in the stomachs which contained gas. The result in one normal dog (unanesthetized), which was injected with a large amount of toxic material from a pneumonic lung, and in two sensitized dogs, which received a very large dose of living virulent pneumococci, should be mentioned in this connection. They all died within 24 hours with a most extensive intestinal hemorrhage, bloody diarrhea, etc., the exact picture of "enteritis anaphylactica" described by Schittenhelm and Weichardt. The stomach contained a moderate amount, the intestine a large amount, of bloody, frothy fluid. Carbon dioxid was demonstrated in both cases, and control tests of the respective materials showed no fermentation. The significance of the presence of carbon dioxid in the stomach and intestine has recently been discussed quite fully by Woodyatt and Graham.¹ Suffice it to say that it is difficult to understand how such a large quantity could accumulate except it be excreted into stomach and bowel from the circulating blood. It should be stated that one of us has found CO₂ in the stomach quite frequently in guinea-pigs which die in from six to 24 hours after injection of toxic pneumococcus extracts and from acute pneumococemia, and that there is present a great tendency to postmortem digestion of the stomach in these animals.

A study of the curves shows that a second toxic dose produces markedly less disturbance than the first dose. In the dogs which received first a nontoxic injection and then a highly toxic dose this insusceptibility is not observed. Renal secretion is practically suspended in the susceptible animal and active in the insusceptible. It is likely that the insusceptibility is explainable on the same basis as antianaphylaxis in general.

Control injections in normal guinea-pigs showed that the appearance and disappearance of toxicity occurs simultaneously for the two species, the striking symptom in the guinea-pig being bronchial spasm while the drop in blood-pressure is the striking

¹ *Trans. Chicago Path. Soc.*, 1912, 8, p. 353.

symptom in the dog, though hemorrhages are more marked in the latter species.

The effect on the respiration is not as marked nor as constant as on blood-pressure. Almost immediately after the injection of toxic material in normal dogs, and of nontoxic heated extract in sensitized dogs which recover, there is a transient increase in amplitude and rate, followed, in a few moments, by a greatly diminished amplitude associated with an inspiratory position of the lungs. This, in turn, is followed by a markedly increased amplitude as the blood-pressure rises. In the animals which succumb, the respiration, when the toxic symptoms begin, is depressed and finally paralyzed. The respiration usually ceases before the heart stops. The increased respiration in dogs which recover is not wholly dependent on return of blood-pressure because the amplitude is greater than before the injection, the blood-pressure still being depressed.

The symptoms and the postmortem changes in dogs are strikingly like those of anaphylaxis. Biedl and Kraus and Pearce and Eisenbrey have shown that in anaphylaxis in the dog the action is peripheral, and Rosenow has shown that the action of the toxic substances in question is also peripheral in normal guinea-pigs. Hence it is likely that the action in dogs following injections of our toxic material is mainly peripheral. The marked cyanosis, the extensive hemorrhages, the delayed coagulation of the blood, and the presence of carbon dioxid in the stomach of the animals which show marked symptoms, speak strongly in favor of the view that, whatever the primary effect of the toxic substances may be, one of the chief results following their injection is interference with oxidation processes. Therefore the increased respiration observed rather late in the animals which recover may well be due to stimulation of the respiratory center by carbon dioxid which accumulates because of the interference with oxidation. In the same way it would seem that, in the animals which succumb, the respiratory center is overstimulated and finally paralyzed. The early and transient inhibitory effect on the respiration would also speak in favor of this view. Detoxication of the material injected

occurs and recovery ensues when the blood becomes thoroughly aerated. This does not occur in the animals which die, cyanosis becoming most extreme.

The pneumonic lung extracts, before they have become acutely toxic and after the toxicity (both for dogs and guinea-pigs) has disappeared, show little or no increase in amino-nitrogen. After long residence at 37° C., however, they show a decided increase and it therefore seems that a certain amount of protein splitting takes place early even though it is not measurable by formol titration. In this respect the lung extracts behave as do pneumococcus extracts and serum mixtures. The toxicity appears and disappears while formol titration shows little or no protein cleavage. Polariscopic measurements, however, show a diminished rotatory power. Except in unimportant particulars the general character of the curves and the lesions produced is strikingly similar, whether the toxic material comes from pneumococci only or from pneumonic lungs and whether formed *in vivo* or *in vitro*. The difference in degree of lesions is due, we believe, rather to a difference in the total dose and concentration at any one time than to a difference in the character of the toxic substances formed. It is of course likely that the lung extracts contain toxic substances which are not present in the extracts of pneumococci. The chief toxic substance, however, is probably identical because of the similarity of symptoms produced and because it appears and disappears under the same conditions in each case. Extracts of pneumococci or of consolidated lungs, which are immediately toxic, are potentially less toxic than those in which free toxic material has not yet been formed, but which is elaborated in the animal after injection. Here all the toxic matter exerts its toxic effects as it is made, whereas during the formation of the toxic material *in vitro* some undoubtedly has gone by the toxic stage at the time of injection and the supply of the substance from which the toxic matter is made is proportionately reduced. Hence the tendency of the animal to recover, provided the initial dose does not kill it outright. That this interpretation is correct seems likely, because after self-digestion continues for a longer time both the immediate as well as the late toxic effects are no longer observed.

CONCLUSIONS.

The action of the toxic substances obtainable from pneumococci and pneumococcus exudates on the blood-pressure and respiration in normal dogs is identical and strikingly like that which is observed in immediate anaphylaxis in dogs. Pneumococcus anaphylaxis in dogs does not essentially differ from protein anaphylaxis in general. The lesions are also similar. The appearance and disappearance of the toxic substance or substances in pneumococcus autolysates and pneumonic lung extracts occurs under the same conditions and simultaneously for dogs and guinea-pigs. In the former species, the striking effect is the marked drop in blood-pressure; in the latter it is the bronchial spasm. Hemorrhages in general, and especially intestinal hemorrhages, are more pronounced in dogs than in guinea-pigs.

The hemorrhages, the effect on the respiration, the extreme grade of cyanosis, especially in the fatal cases, the delayed coagulation of the blood, and the presence of carbon dioxide in the stomach indicate that one of the chief effects of the toxic substances is an interference with the normal oxidative processes. The toxic substances concerned are probably of the same general nature because the lesions and the effect on the circulation and respiration are so similar, and it makes no essential difference whether they are formed *in vitro*, in the consolidated lung in man, at once in sensitized dogs, or at a later period in normal dogs.

EXPERIMENT I.

EFFECT OF THE INJECTION OF TOXIC PNEUMOCOCCUS EXTRACT (No. 300) ON THE
BLOOD-PRESSURE AND RESPIRATION.
Female dog, weight 8 kilos. Ether anesthesia.

TIME	INJECTION	BLOOD-PRESSURE	RESPIRATION	
			Rate	Amplitude
Hrs. Min.				
12 25.....	Injected about 15 c.c.	144 mm.	45	14 mm.
12 27.....		64	50	19
12 30.....	Injected 6 oz. 12:29 to 12:31	126	48
12 32.....		44	42	8
12 37.....		44	54	20
12 45.....	Injected 7 oz. 12:45 to 12:47	60	63	25
12 48.....		82	75	30
12 52.....		112	70	29
12 58.....		128	60	25
1 10½.....		132	55	25

Dog was killed at 1:20 P.M.

Autopsy.—The heart is dilated with blood. The musculature is quite soft. There are no visible hemorrhages in the endocardium. The lungs present several areas of hemorrhage, especially in the dorsal portion of the lobes. These are about one centimeter in diameter. The lungs float on the surface of water. There is a marked congestion of the right posterior lobe.

The stomach is greatly distended with gas which gives the test for carbon dioxide (lime-water test). There are no hemorrhages. The spleen is somewhat darker than normal. The kidneys are somewhat enlarged; the cortex is especially thickened and rather cloudy; the cortical striations are rather indistinct. The capsule strips readily. There seems to be a marked congestion of both kidneys. The liver, pancreas, etc., appear unchanged.

Microscopical changes.—There is a moderate grade of hyperemia of the villi in the intestine. The kidney presents marked changes; many glomeruli contain blood within the Bowman's capsule; some of the glomerular tufts are distended with blood; in other areas there are circumscribed hemorrhages which seem to occupy the spaces of Bowman's capsule. There are other hemorrhages in the cortex and few between the tubules. In the lung is found a very striking condition of hemorrhages, surrounding the larger vessels, especially veins. Some of these are so extensive as to surround the vessel completely, forming a ring of blood in the loose connective tissue. There are hemorrhages into the alveoli in many areas. The spleen shows a marked congestion. In the heart muscle can be found a few small hemorrhages between the muscle fibers. The other organs present no changes.

EXPERIMENT 2.

EFFECT OF THE INJECTION OF AUTOLYZED PNEUMOCOCCUS EXTRACT (No. 301)

AFTER TOXICITY FOR GUINEA-PIGS HAD DISAPPEARED.

Female dog, weight 11 kilos. Ether anesthesia.

TIME		INJECTION	BLOOD-PRESSURE	RESPIRATION	
				Rate	Amplitude
Hrs.	Min.				
10	26.....	Injection of 5 oz. from 10:26 to 10:27½	144 mm.	66	10. mm.
10	27.....		132	..	9.
10	27½.....		139	..	9.
10	28.....		132	74	10.
10	30.....		151	66	10.
10	32.....		154	64	11.5
10	40.....		158	63	12 (av.)
11	05.....		161	58	11.5 (av.)

Autopsy.—Since a second injection of a toxic extract was made in this animal not shown in the curve, and which caused a marked fall of blood-pressure, the changes in the organs were not carefully studied.

EXPERIMENT 3.

EFFECT OF THE INJECTION OF UNAUTOLIZED LIVING VIRULENT PNEUMOCOCCI
ON THE BLOOD-PRESSURE AND RESPIRATION.
Male dog, weight 9 kilos. Ether anesthesia.

TIME		INJECTION	BLOOD-PRESSURE	RESPIRATION	
				Rate	Amplitude
Hrs.	Min.				
1	04.....	Injection of 1 oz. of suspension (containing 700 billions in salt solution.) Time of injection 20 seconds.	152 mm.	52	11. mm.
1	05.....	54	86	14. (Expiration forcible.)
1	08.....	70	60	12.
1	10.....	92	58	12.
1	13.....	100	62	14.
1	17.....	106	64	19.
2	00.....	124	62	32.
2	30.....	116	56	14.
3	22.....	82	52	27.
3	30.....	78	52	30.
3	40.....	76	54	28.
5	46.....	60	40	13.
5	49.....	59	35	10.
5	53.....	59	32	11.5
5	56.....	59	..	11.

Autopsy.—The heart is greatly dilated, soft, somewhat flabby. There are subepicardial hemorrhages, from a pin-point to 0.5 cm. in diameter, over the left ventricle, especially near the apex. The inner wall of the left ventricle is covered with subendocardial hemorrhages, varying from one or two millimeters to one centimeter in diameter. These are most marked over the papillary muscles, one of which is capped by a large, deep hemorrhage. Some hemorrhages extend to the attachments of the mitral valve; they are very numerous on the septal wall of the left ventricle. There are no visible subendocardial hemorrhages in the right heart. The right posterior lobe of the lung is very dark red and sinks in water; there is a thick bloody mucus in the bronchi; the rest of the lung is collapsed. Other lobes are redder than normal and less crepitant. The peribronchial glands are enlarged. The liver is dark in color, but there are no other visible changes. The stomach is distended with gas, and contains food; CO₂ test positive; the veins are especially enlarged. The kidneys contain a large amount of blood; the cortical markings are distinct. In the intestines there is present a small amount of bloody mucous fluid. The lymph follicles are large and hyperemic. There are small areas of mucosa which are red in color and there appear to be hemorrhages.

Microscopical changes.—Changes are most numerous in the heart. There are hemorrhages in the papillary muscles, which are most often near the junction of the muscle fibers with the fibrous tissue, between the fibers, and which have a tendency to run parallel with the muscle fibers, communicating with each other. Some of the hemorrhages are just beneath the endocardium. In the lung are numerous hemorrhages; many of the alveoli and bronchioles are filled with blood. There are perivascular hemorrhages in the liver; these are chiefly about the portal veins in the portal canals. Some of the veins are surrounded by blood which has dissected the loose connective tissue. In the villi of the intestine there is marked hyperemia so that the capillaries appear to be on the surface of the villi. The ends of the villi are chiefly

affected, and here one can see the ring of dilated capillaries at the circumference of the villus with the large central capillary, but no hemorrhage is present. In the cortex of the kidney are numerous hemorrhages, mostly about three times the size of a Malpighian body. Some of the glomeruli are filled with blood. There are some hemorrhages between the tubules. There are small hemorrhages in the cortex of the adrenal and the medulla is congested.

EXPERIMENT 4.

EFFECT OF THE INJECTION OF AUTOLYZED VIRULENT PNEUMOCOCCI ON THE
BLOOD-PRESSURE AND RESPIRATION.

Female dog, weight 8 kilos. Ether anesthesia.

TIME		INJECTION	BLOOD-PRESSURE	RESPIRATION	
Hrs.	Min.			Rate	Amplitude
2	39.....	Injection of 6 oz. (containing 700 billions in salt sol.) from 2:39 to 2:40½	140 mm.	86	13. mm.
2	40.....		137	...	9.
2	40½.....		142	106	9.
2	45.....		135	90	12.5
2	50.....		140	96	10.
3	10.....		140	100	11.
3	40.....		134	88	10.5
3	42.....		133	...	10.5

Dog was killed at 4:00 P.M.

Autopsy.—There are no marked changes in the lungs. Two or three small areas of hemorrhage are present on the surface, about five millimeters in diameter. There are a few petechiae over the region of the interventricular septum. The abdominal organs are unchanged. The stomach contains no gas. Microscopically no changes are present in any of the organs, except for a few hemorrhages in the lungs and heart muscle.

EXPERIMENT 5.

EFFECT OF THE INJECTION OF HEATED UNAUTOLYZED PNEUMOCOCCUS EXTRACT
(NO. 302) ON THE BLOOD-PRESSURE AND RESPIRATION OF SENSITIZED DOG.

Male dog, weight 7 kilos. Ether anesthesia.

TIME		INJECTION	BLOOD-PRESSURE	RESPIRATION	
				Rate	Amplitude
Hrs.	Min.	Injection of 5½ oz. of extract from 2:55 to 2:56½	98 mm.	50	5. mm.
2	55.....				
2	55½.....				
2	55¾.....				
2	56¼.....				
3	00.....				
3	06.....				
3	11.....				
3	24.....				
3	27½.....				
3	50.....				
3	55.....				

Dog was killed at 4:00 P.M.

Autopsy.—There are several areas of hemorrhage in the lungs, some as large as two centimeters in diameter. There is some edema of the lungs. The heart is dilated and quite soft. The liver is dark in color, with marked congestion. The stomach is distended with gas, carbon dioxid test positive. There are no visible changes in the bowels except a moderate congestion. The cortex of the kidney is pale, but distinct.

EXPERIMENT 6.

EFFECT OF THE INJECTION OF EXTRACT (No. 637) OF PNEUMONIC LUNG (IN SALT SOLUTION) ON THE BLOOD-PRESSURE AND RESPIRATION.

Female dog, weight 7 kilos. Ether anesthesia.

TIME	INJECTION	BLOOD-PRESSURE	RESPIRATION	
			Rate	Amplitude
Hrs. Min.				
2 30.....	Injection of 4 oz. of extract from 2:30 to 2:32½	136 mm.	55	12. mm.
2 30½.....		160	..	12.
2 30½.....		72	..	10.
2 30½.....		102	..	160.
2 30½.....		66
2 31½.....		78	46	90.
2 32.....		52	62	10.
2 33.....		48	55	0.4
2 36.....		42	65	12.
2 39.....		50	55	13.
2 45.....		64	58	50.
2 48.....	Injection of 4 oz. of extract from 2:48 to 2:50	78	60	50.
2 48½.....		92	..	40.
2 48½.....		52	..	40.
2 50.....		103	80	80.
3 00.....		103	70	40.

Autopsy.—The heart is filled with a large amount of blood. There are several areas of subendocardial hemorrhages of from one to five millimeters in diameter, scattered chiefly through the right ventricle, especially about the papillary muscle; there are few hemorrhages in the left ventricle. The lungs are markedly congested, especially in the dorsal portions. A few areas of probable hemorrhage can be seen on the surface. The stomach is large and distended with gas. There are many irregular hemorrhages under the serosa; these are light red in color and resemble exudations. The splanchnic vessels are greatly distended, especially the mesenteric veins. Some bloody fluid is present in portions of the mesentery, near its attachment to the bowel. On incision, the small bowel is found to be filled with a bloody, frothy fluid. The mucosa is covered with a sticky mucus which almost forms a membrane. On clearing the surface many large elevated blood-stained regions are found scattered through the bowel, varying in size from one-half to two centimeters in diameter. Some are ovoid, with their long diameter longitudinal. There are also a few small defects in the mucous membrane. The mucosa is covered in large areas with small and large submucosal hemorrhages, which are present through almost the entire bowel. The pancreas is studded with petechial hemorrhages. The spleen is dark in color. The liver is dark, and a large amount of blood exudes from the cut surfaces. The kidneys are congested, especially the cortex near the medulla. The adrenal medulla is very dark in color.

Microscopical changes.—In the lymphoid follicles of the intestine are numerous hemorrhages, some so large as to occupy almost the entire follicle. The centers of all the follicles are filled with blood. There are also submucosal hemorrhages, and hemorrhages between the villi. There are large hemorrhages in the mesenteric lymph glands. In the lungs are large hemorrhages about some of the larger vessels. The spleen is markedly congested and hemorrhagic. The hemorrhages are more numerous about the vessels. There are minute hemorrhages scattered through the heart muscle, between the fibers; there are also a few large hemorrhages. There are many small distinct hemorrhages in the adrenal cortex, and the medulla is congested. A few irregular regions of hemorrhage are found in the liver. In the kidney are numerous hemorrhages in the cortex, many into the glomeruli. These are mostly large, round or oval, circumscribed regions. There are hemorrhages in the medulla between the tubules. Some of the tubules contain blood.

EXPERIMENT 7.

EFFECT OF THE INJECTION OF SECOND EXTRACT OF PNEUMONIC LUNG (No. 639), AS
SOON AS MADE, ON THE BLOOD-PRESSURE AND RESPIRATION.
Female dog, weight 10 kilos. Ether anesthesia.

TIME		INJECTION	BLOOD-PRESSURE	RESPIRATION	
				Rate	Amplitude
Hrs.	Min.				
3	00.....	Injection of 5½ oz. of extract from 3:00 to 3:02½	148 mm.	48	15. mm.
3	02½.....	142	44	17.
3	07.....	160	39	15.5
3	11.....	Injection repeated	162	38	16.
3	13½.....	148	46	15.
3	17.....	158	40	13.
3	30.....	168	30	11.
3	45.....	179	20	6.
3	51.....	150	14	7.5
3	56.....	132	10	11.
4	00.....	94	6	10.
4	02.....	Heart stopped	10
4	04½.....	Respiration ceased

Autopsy.—The heart is greatly dilated and very dark in color; the coronary veins are very distinct and dark in color. The blood is almost blue. The lungs are collapsed. There is passive hyperemia of the dorsal borders. The stomach is large and distended with gas, CO₂ test positive. The mesenteric veins are greatly distended, dark blue and distinct. The liver is extremely dark, bluish-purple in color, and contains a large amount of blood. The pancreas and spleen appear normal. The veins of the renal capsule are very distinct; the capsule strips readily, disclosing small circumscribed dark regions in the cortex. There are no other changes.

Microscopical changes.—There are small hemorrhages in the lung, chiefly beneath the pleura. The bronchial glands are normal. There are large perivascular hemorrhages in the pancreas, especially about the larger vessels, also minute hemorrhages between the gland-cells and into the connective tissue. The kidney presents numerous hemorrhages, chiefly in the cortex; in some regions the glomeruli are filled with blood and even distended, so that the glomerular tuft is not seen. The liver shows a high grade of hyperemia, the congestion being chiefly in the centers of the lobules. The capillaries and veins of the heart muscle are greatly distended.

EXPERIMENT 8.

EFFECT OF THE INJECTION OF THE SECOND EXTRACT OF PNEUMONIC LUNG (No. 639),
AFTER ON ICE FOR 24 HOURS, ON THE BLOOD-PRESSURE AND RESPIRATION.
Female dog, weight 5.2 kilos. Ether anesthesia.

TIME		INJECTION	BLOOD-PRESSURE	RESPIRATION	
				Rate	Amplitude
Hrs.	Min.				
12	16.....	Injection of 2½ oz. of extract from 12:16 to 12:17	113 mm.	95	7. mm.
12	16½.....		117	90	6.5
12	16¾.....		106	85	6.5
12	17.....		110	95	7.
12	22.....		111	90	6.
12	27.....		103	98	4.5
12	30.....	Injection of 3½ oz. of extract from 12:30 to 12:34	110	88	5.
12	34.....		112	80	5.
12	40.....		126	70	4.
12	45.....		127	56	4.
12	49.....		124	52	3.8
1	00.....		130	44	2.8
1	05.....		124	36	2.
1	08.....		114	40	1.8
1	11.....		93	36	1.5
1	14½.....		49	30	1.5
1	15.....		41	15	2.
1	16.....	Respiration ceased
1	17.....	Heart stopped	0

Autopsy.—There are no lesions, except for the dilated heart and congestion of the dorsal portion of the lung.

Microscopical changes.—There are frequent hemorrhages in the renal cortex; some seem to be in Bowman's capsule. The capillaries and veins of the heart muscle are dilated.

EXPERIMENT 9.

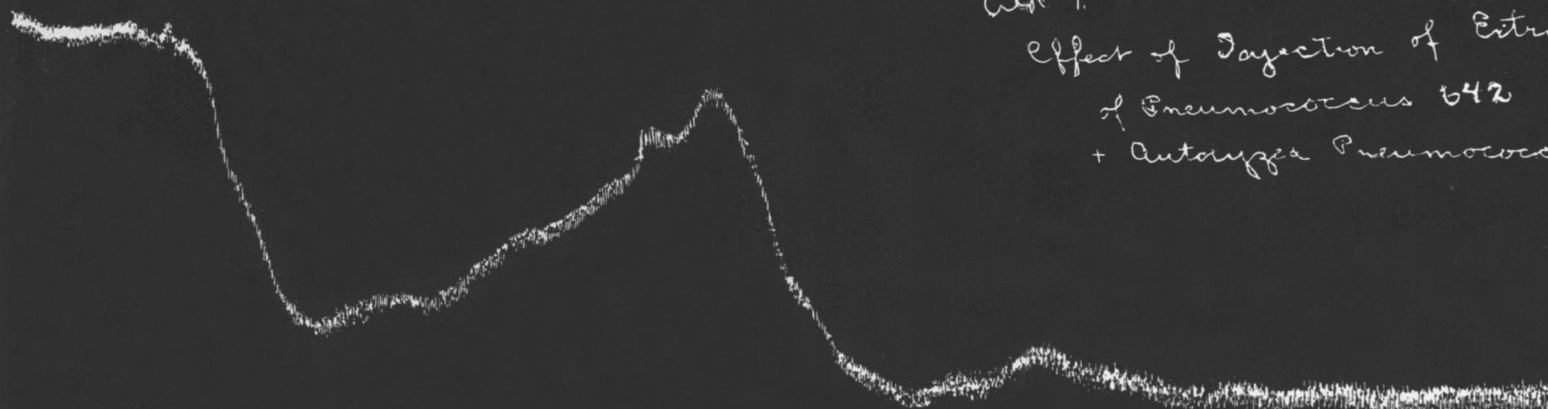
EFFECT OF THE INJECTION OF LUNG EXTRACT (No. 649) AFTER 18 HOURS AT 37° C.
PLUS GROWTH FROM 300 C.C. BROTH CULTURE OF PNEUMOCOCCUS ON THE
BLOOD-PRESSURE AND RESPIRATION.
Male dog, weight 8 kilos. Ether anesthesia.

TIME		INJECTION	BLOOD-PRESSURE	RESPIRATION	
				Rate	Amplitude
Hrs.	Min.				
12	24.....	Injection of 6 oz. of extract from 12:24 to 12:25	100 mm.	50	9. mm.
12	24½.....		107
12	24¾.....		47	62	11.
12	25½.....		68	72	12.
12	27½.....		87	66	8.
12	31.....		41	62	11.
12	36.....		34	70	13.
12	44.....		42	68	15.
1	38.....		32	45	10.5
2	05.....		29	32	5.
2	37.....		22	8	6.
2	48.....	Respiration ceased
2	54.....	Heart stopped

12 25
P.M.

Began with
Inj. of about 150 c.c.
Stopped on account
of cat & bulb

12 28
P.M.



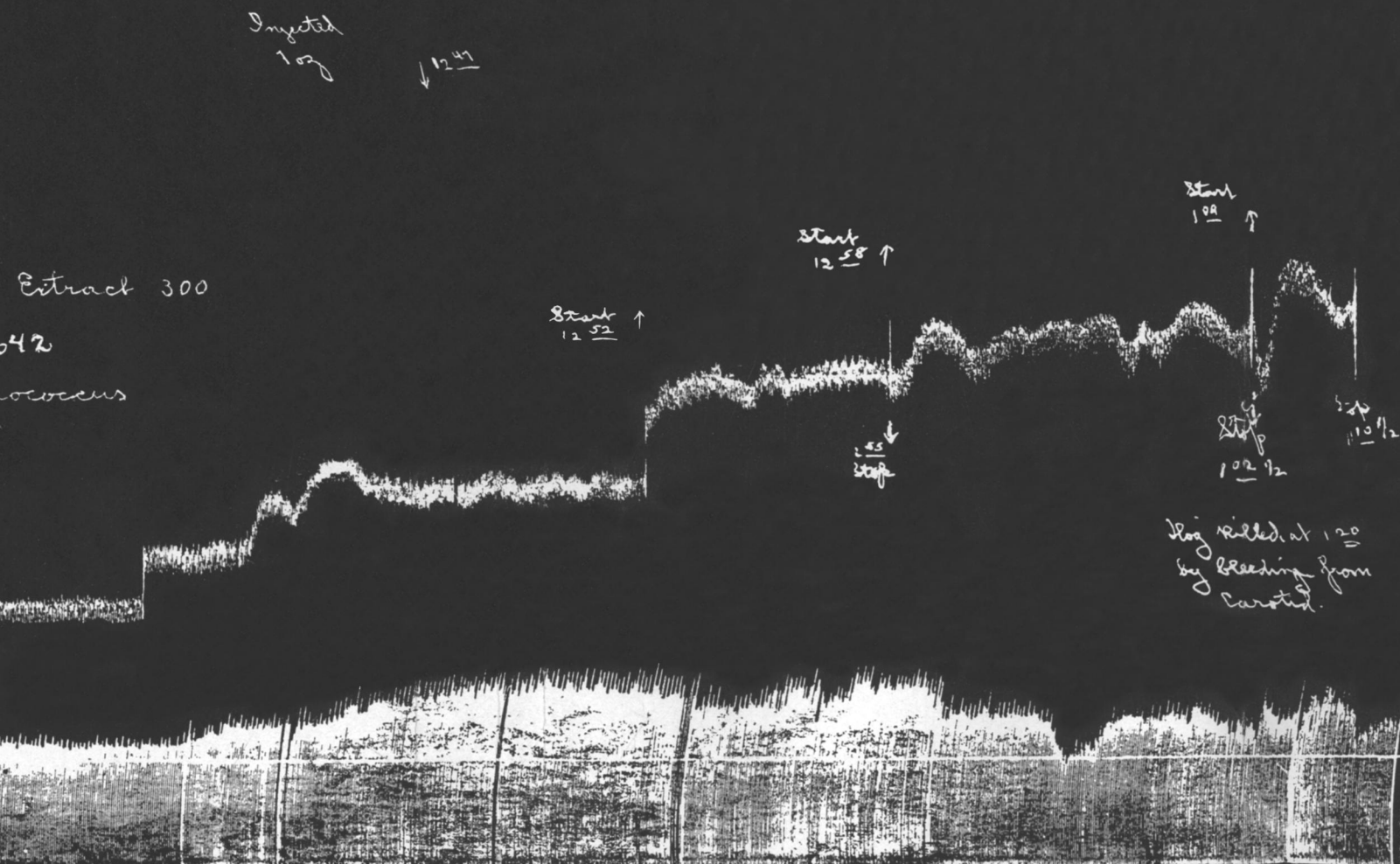
BASE LINE

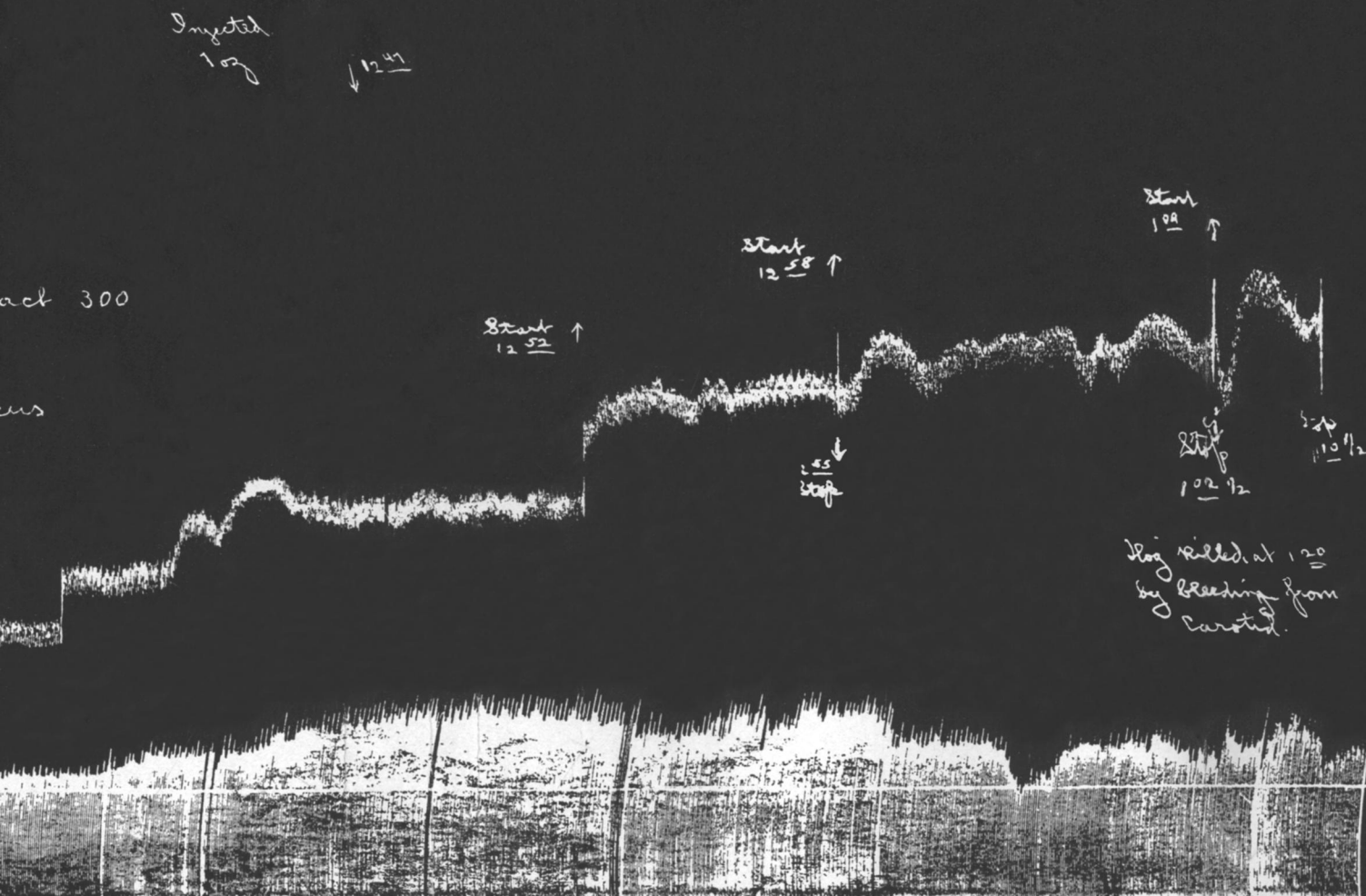
EXP 1.

Effect of Injection of Extract
of *Pneumococcus* 642
+ Autolyzed *Pneumococcus*

Feb. 16, 1912 —

EEB E





10 26
9 mpc.
Begin

50g.

10 27 1/2
9 mpc.
End



Exp 2

Effect of Injection of Autolysed
Pneumococcus Est. 301, after
toxicity for guinea-pigs had
disappeared

Don - Female - 11 Kilos.

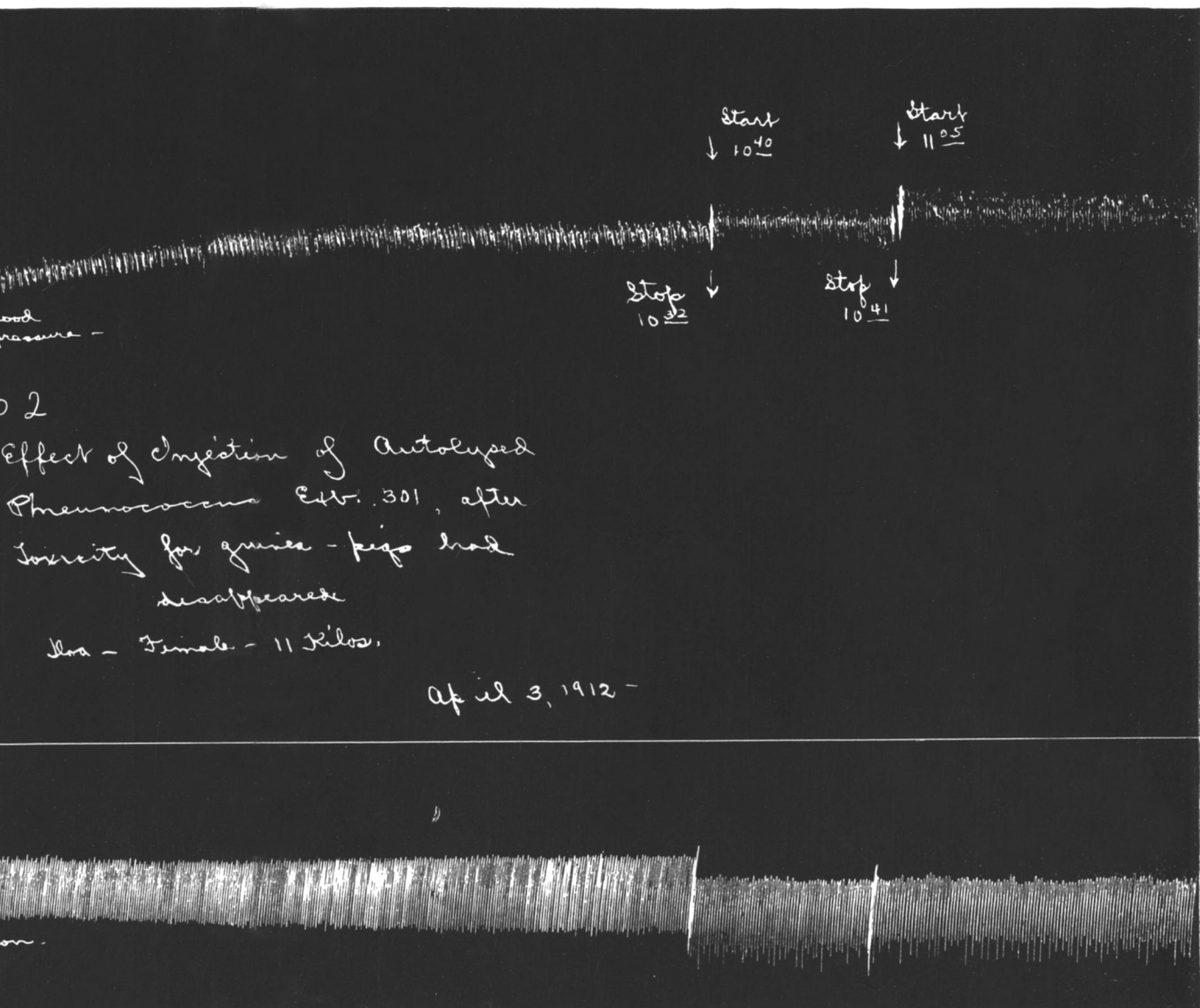
April 3, 19

Base line



Respiration -

PLATE 5.



104 P.M.
↓ Directed
100 Grams
in 20 sec.

Black press

Exp. 3

Effect of Injection of
Virulent Pneumococci
in dog intravenously -
(1 cc of Suspension from 800
cc. of Broth culture)

dog, male, 9 kilo

March 15 1912 -

(No. 1)

Ref. 1

Exp 3 - Continued

Blood press

↓
340 start

343
stop ↓

↓ 546 start

Respir

(no
m

547

548

549

LATE 7.

↓ 555
Start

556
stop

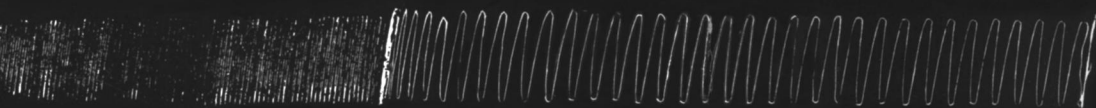
↓
stop
557

1 minute

log killed
at 6 p.m.

(no 2)

march 15 1912



2-29
↓ began
injec bag

2 40 1/2
↓ Saps
ambal

Blood
pressure

Exp 4

Effect of Injection of Autoly

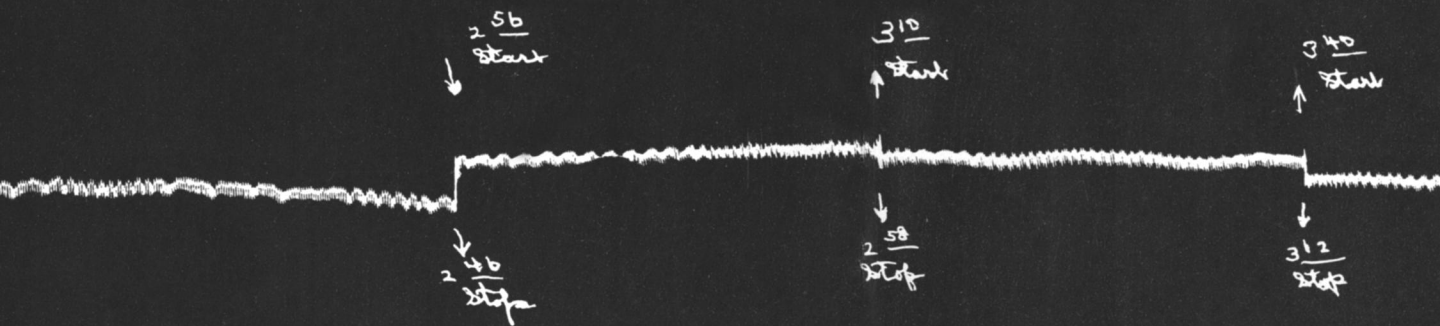
Pneumococci in Hog (trans)

amb injected = 700 billions

Apr

base line

Respir.



utilized "ruler"
(female, 8 Kilo)
lines in 6 oz. Del pol

April 2, 1912 -

56
Start

310

↑ Start

↓

2 58

Stop

340

↑ Start

↓

312

Stop

372

Stop

dog Killed at 48m
Brain cut.

2 55

5 mgc.

5 1/2 mg

Est

5 mgc

ended

2 56 1/2

3 06 pm

Stop

30 sec ↓

Blood pressure

base line

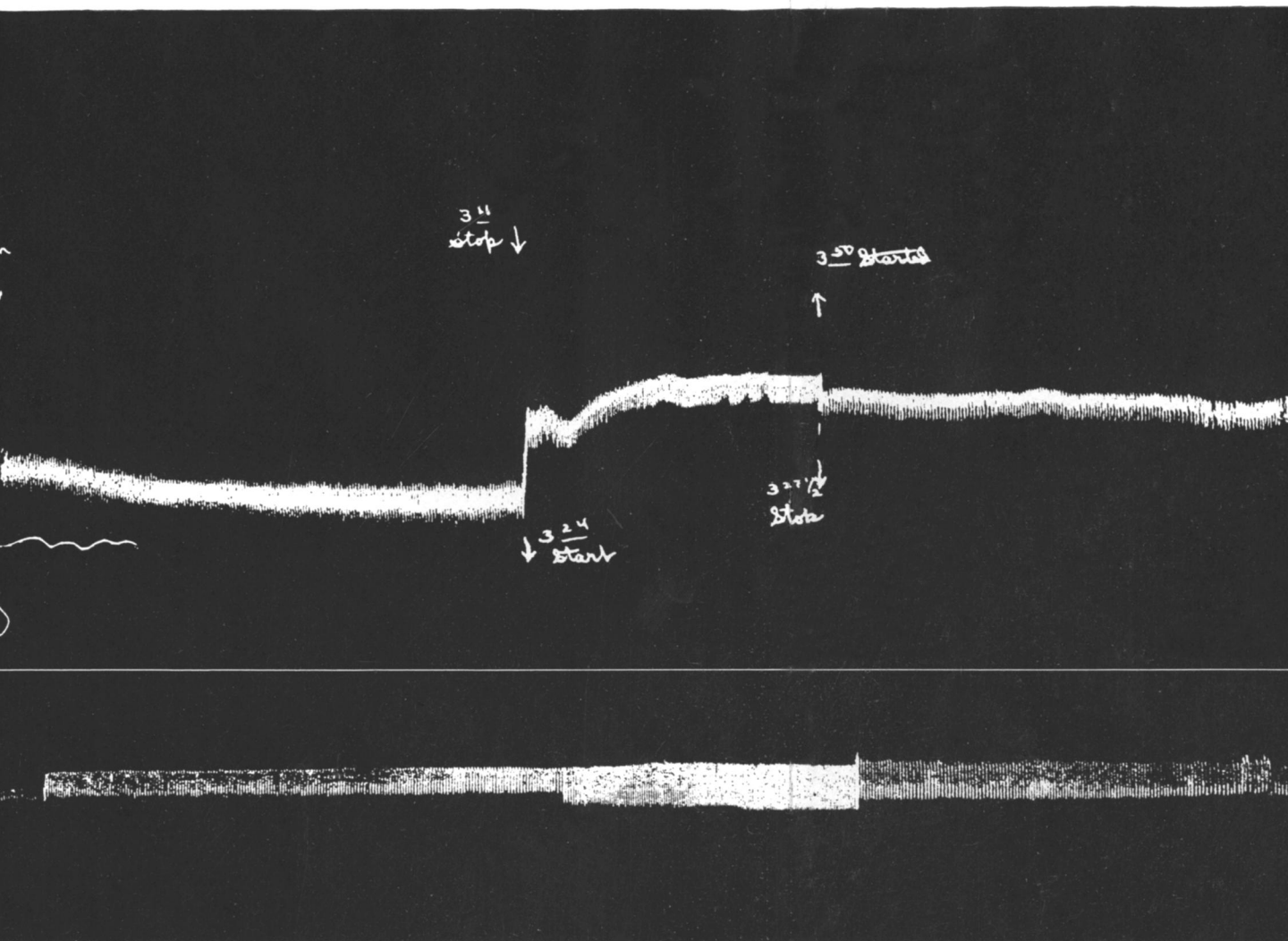
Exp. 5

Effect of Injection of Heated
Pneumococcus Est (+302) on
Sensitized Dog (mab, 7 Kilo)

Respir

March 7 1912—

PLATE 9.



3¹¹
stop ↓

3⁵⁰ started

↑

3⁵⁵
stop ↓

3²⁴
start ↓

3^{27 1/2}
stop ↓

log killed
at 4⁰⁰ pm

↓ Injected 4 ounces
of Extract
23 P.M.

↓ Injection
ended

Exp 6.

Effect of Injec. of Extract of Pneumonia lung
(in salt solution) on Blood Pressure and

Respiration of Dog (Female, 7 kilo)

Ext. No. 637.)

Blood pressure (right Carotid)

base line

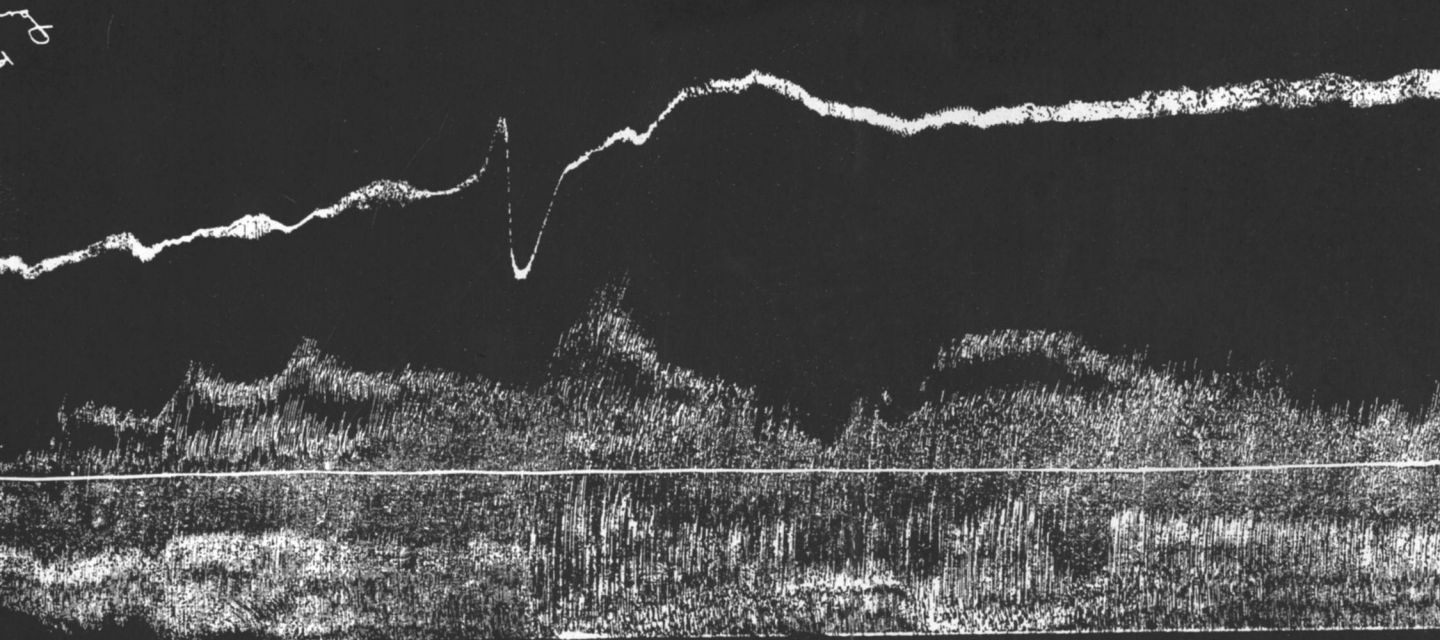
Respiration

Feb 3, 1912

↓ Projected
+ success
of E. road

↓ Inge.
creek

↓ 3 minutes



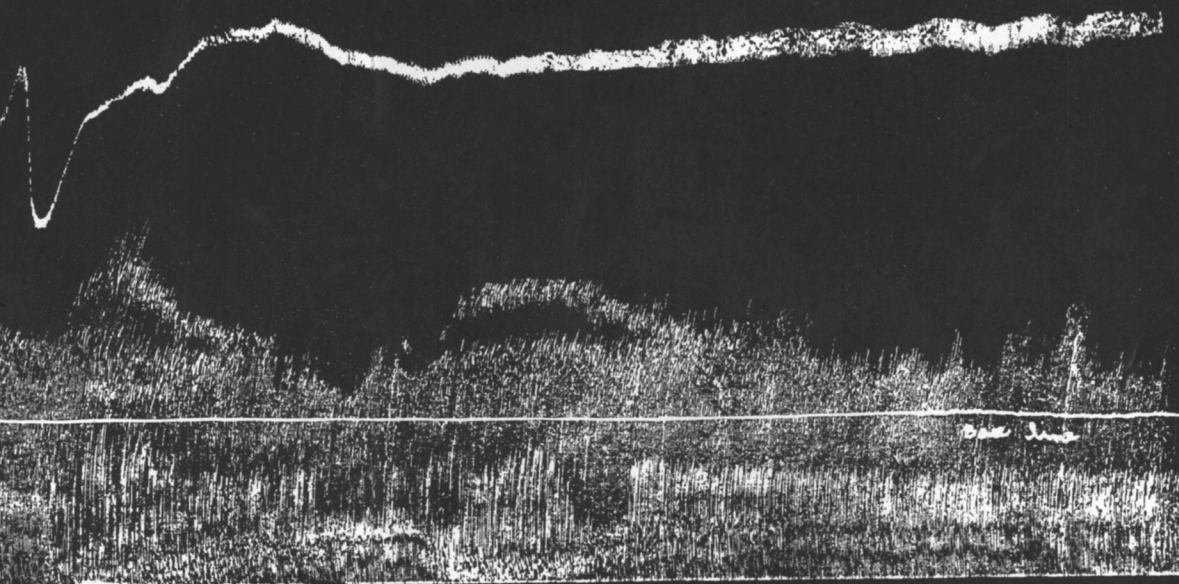
projected
+ success
of trial

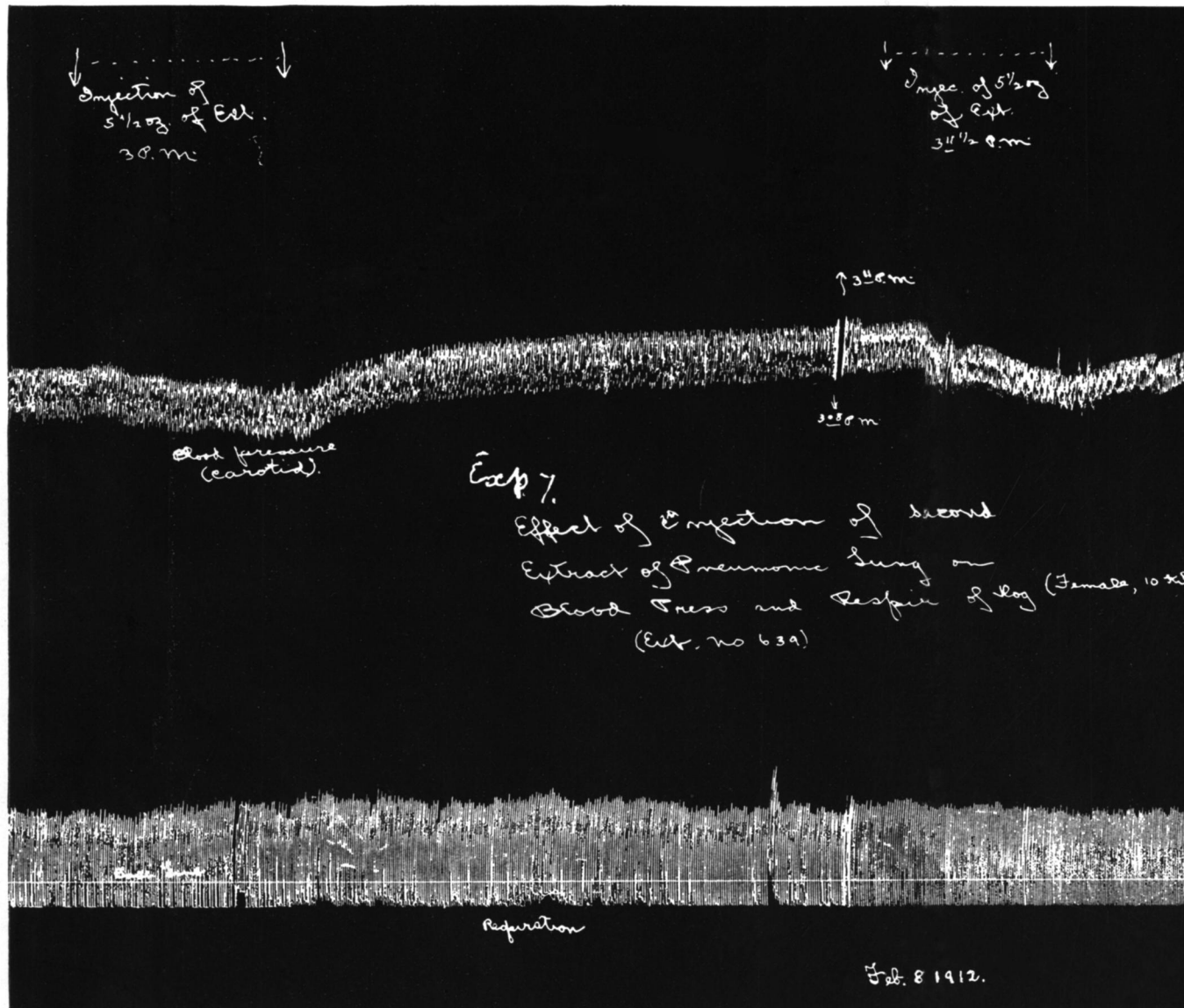
↓ Inge.
cubed

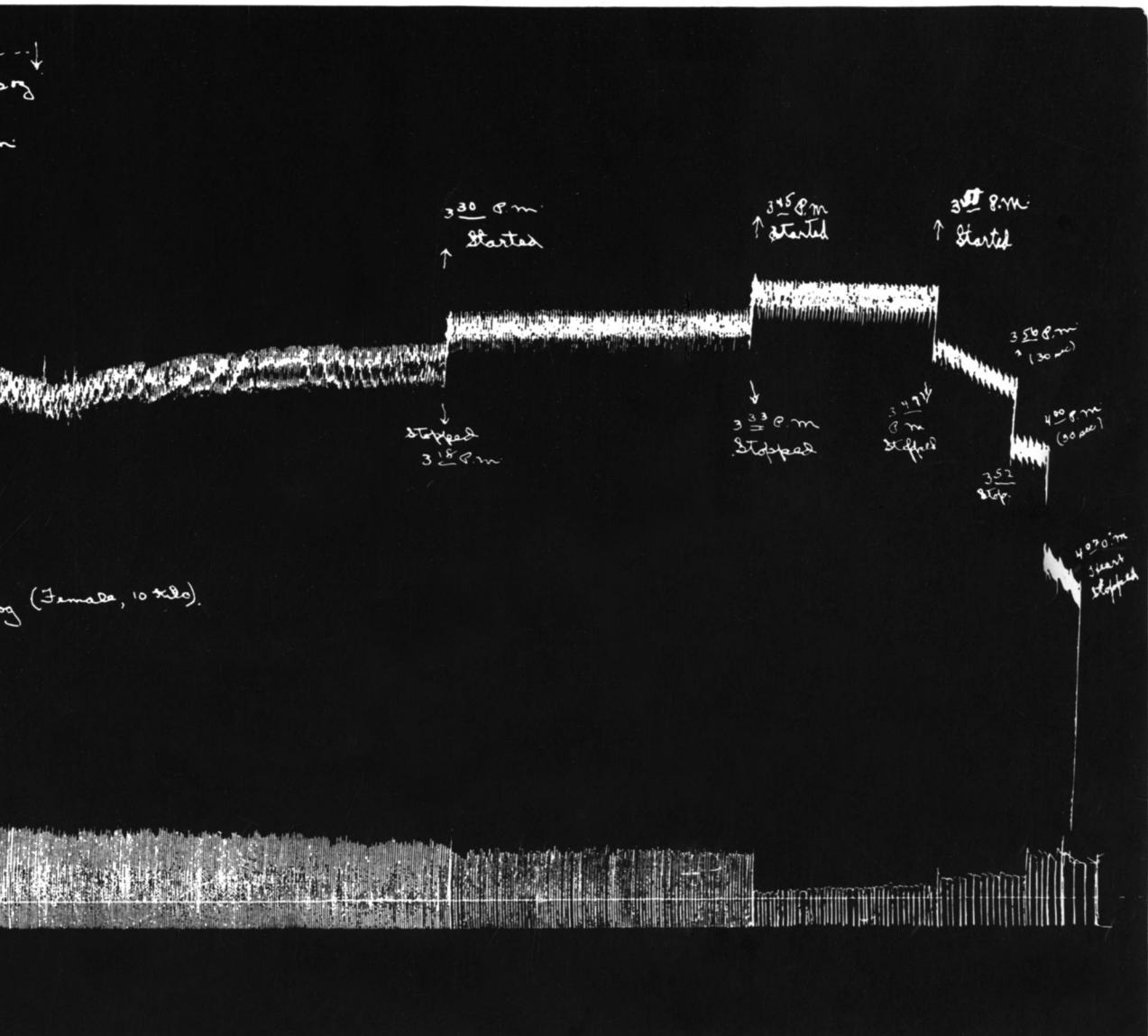
↓ 3 minutes

↓
3:00 P.M.
removed
them

log killed at
3:00 P.M.







↓ - - - ↓
Sugar
2 1/2 oz.
12³⁰ P.M.

↓ - - - - -
Injection of
12³⁰ P.M.

Blood pressure

Exp. 7. Effect of
of new
Blood

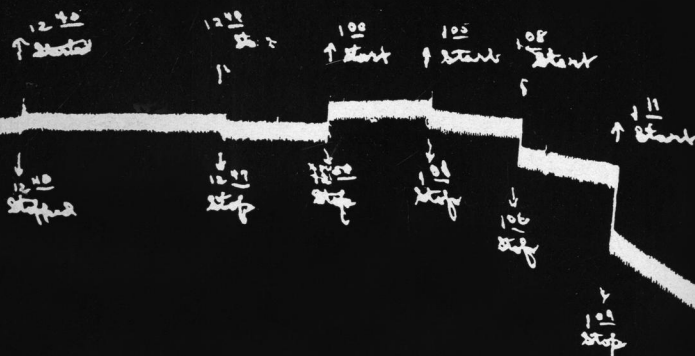
Respiration

one line

on of 3 1/2 oz. ↓

Effect of Injection of Second Extract
of Pneumonia Bury (back dot) on
Blood Press and Respire of Dog
(Amale, 5.2 kilo)

Expt. No. 639.



Feb 9, 1912

Extract
(on
of log

$12 \frac{30}{20}$
↑ Start

↓
 $12 \frac{40}{20}$
stop

$12 \frac{45}{20}$
↑

↓
 $12 \frac{50}{20}$
stop

100
↑ Start

↓
 100
stop

100
↑ Start

↓
 100
stop

108
↑ Start

↓
 106
stop

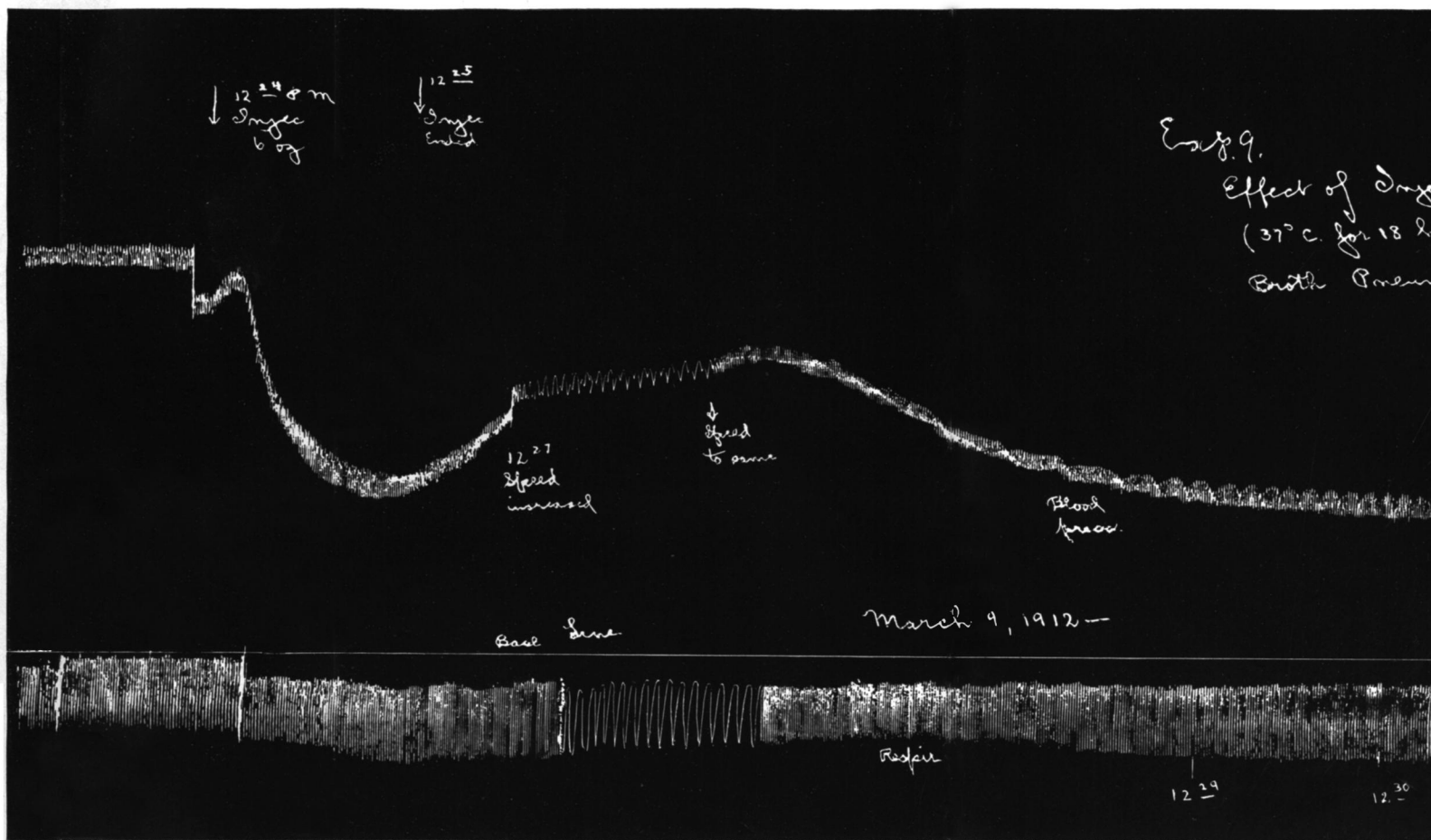
↑
 11
Start

↓
 100
stop

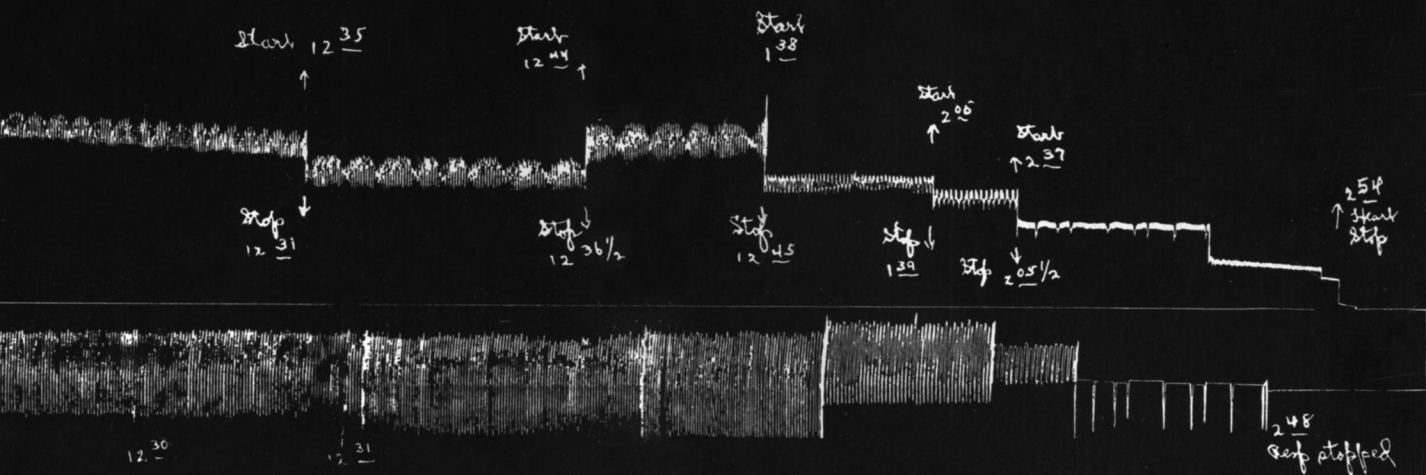
↑
 115
Start

↓
 $114 \frac{1}{2}$
stop

↓ 2 mm. ↓



fect of Injection of Lung Ext 649
 37°C for 18 hrs) + Growth from 300 cc
 Broth Pneumococcus (Day 2)



Injection of
5 cc Extract

↓ 12, 32 1/2
P.M.

↓ 12 42
P.M. 5 cc

Stop
12 37 1/2
P.M.

Start
↑ 12 41
P.M.

Blood
Pressure

Exp. 10

Effect of Injection of Extract of
Pneumonic Lung on Blood Press.
and Respiration of Dog (Female, 8 Kilo
(Ex. 639 - after 5 days at 37°C.).

Base Line

Respir.

Feb. 13, 1912.

Injection of
5 cc Extract

↓ 12, 32 1/2
P.M.

↓ 12 42
P.M. 5 cc

Stop
12 37 1/2
P.M.

Start
↑ 12 41
P.M.

Blood
Pressure

Exp. 10

Effect of Injection of Extract of
Pneumonic Lung on Blood Press.
and Respiration of Dog (Female, 8 Kilo
(Ex. 639 - after 5 days at 37°C.).

Base Line

Respir.

Feb. 13, 1912.

Autopsy.—The lungs are collapsed, of a somewhat leathery consistency, and dark red in color, especially on the dorsal surface. The cut section has a leathery appearance and is quite bloody. The heart is markedly dilated, and soft. The intestines on cross-section show what appears to be submucous hemorrhage involving the entire circumference of the bowel. There is a large amount of frothy fluid in the intestine, which is partly bloody. The stomach is distended with gas and a frothy greenish fluid. The other organs present no gross changes.

Microscopical changes.—The villi of the intestine present an extreme capillary dilatation, so that the capillaries lie on the surface of the villi. These form a ring beneath the surface almost in contact with each other, with one dilated central capillary, whereas in the normal intestine capillaries are found with difficulty. The entire circumference of the bowel presents this beautiful picture of congestion. There are also many hemorrhages at the ends of the villi and in the submucosa. In the pancreas there is a congestion of the capillaries and veins. There are a few small hemorrhages. In the lung the hemorrhages are most marked. Many regions contain alveoli filled with blood. Some of the bronchioles also contain blood. In the liver are a few small hemorrhages between the liver cells, with some congestion. The spleen is markedly congested and contains hemorrhages. In the heart muscle are congested capillaries and venules with a few small hemorrhages between the muscle fibers.

EXPERIMENT 10.

EFFECT OF THE INJECTION OF AUTOLYZED EXTRACT OF PNEUMONIC LUNG (No. 639),
AFTER FIVE DAYS AT 37° C., ON THE BLOOD-PRESSURE AND RESPIRATION.

Female dog, weight 8 kilos. Ether anesthesia.

TIME	INJECTION	BLOOD-PRESSURE	RESPIRATION	
			Rate	Amplitude
Hrs. Min.				
12 30.....	Injection of 5 oz. of extract from 12:30 to 12:32½	119 mm.	48	10. mm.
12 32½.....		112	50	12.
12 34.....		122	56	10.
12 37.....		124	56	10.5
12 41.....		125	54	10.
12 42.....	Injection of 5 oz. of extract from 12:42 to 12:44
12 44.....		110	60	7.
12 52.....		124	60	10.
1 02.....		126	56	10.5
1 15.....		128	56	10.5
1 31.....	Dog killed	127	60	11.
1 42.....		128	60	10.
2 00.....		128

Autopsy.—There are no macroscopic or microscopic changes visible in any of the organs.

EXPLANATION OF PLATES 4-14.

Curves of Respiration in Dogs 1-10.